0021-972X/85/6006-1221$02.00/0
Journal of Clinical Endocrinology and Metabolism

Vol. 60, No. 6
Printed in U.S.A.

Alterations of Mental Status and Thyroid Hormones after Thermal Injury*

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ABSTRACT. In 16 burn patients, mean values for serum T_4 and T_3, their T_3 uptake-derived free indices (FT_4I and FT_3I) and dialysis-derived free concentrations (FT_4 and FT_3) were depressed (all $P < 0.001$) compared to respective means in 13 normal subjects. In the patients, the free hormone indices were relatively more depressed below control values than were the free hormone concentrations. However, within the group of burn patients, variation in FT_4I reflected that of FT_4 ($r = 0.91$), and variation in FT_3I reflected that of FT_3 ($r = 0.93$). We then studied serum T_4, T_3, and their free indices in 134 patients (burn size, 6–96% of the skin area), including 45 nonsurvivors, none of whom received steroid, dopamine, or iodine treatment. At each sampling, the level of obtundation (LO) was determined on a 6-point scale from normal to deep coma. Whereas initially low mean FT_4I values rose in survivors, they remained lower in nonsurvivors than in survivors until death in the nonsurvivors. In nonsurvivors, mean LO worsened in the first week and remained worse than that in survivors until death. Multiple regression analyses showed that for a given age or burn size, nonsurvival was better correlated with lower T_4 or FT_4I than with T_3 or FT_3I, but was even more closely correlated with worse LO ($P < 0.001$). Exclusion of data obtained within 24 h of narcotic or tranquilizer doses did not weaken the relationship of nonsurvival with LO and FT_4I. Nonsurvival after burn injury was associated with reduced T_4, FT_4I, and mental status for up to weeks before death, this association being independent of treatment with drugs acting on mental status or thyroid function. (*J Clin Endocrinol Metab* **60:** 1221, 1985)

T_4 AND T_3 concentrations in serum may be depressed in burn patients (1–3), similar to thyroid hormones in patients with many other types of nonthyroidal illness (NTI) (4, 5). Previous studies of a variety of NTI patients (6–8) suggested that low serum T_4 concentrations were particularly related to nonsurvival. We sought to determine whether mental status is related to serum thyroid hormone values in burn patients and whether these variables are related to outcome.

Subjects and Methods

Morning serum samples were obtained approximately once per week for thyroid hormone and other routine chemical determinations in patients in the intensive care areas of our burn unit. These patients were treated with fluids and electrolytes for initial resuscitation and subsequent evaporative loss and were provided with vigorous nutritional support (2), alternating topical mafenide acetate and silver sulfadiazine, systemic antibiotics if needed for infection, morphine (occasionally meperidine) as needed for pain, and antacids and occasionally cimetidine to prevent Curling's ulcers, and excision and grafting of wounds were performed when indicated. Treatment did not include topical or systemic agents containing iodine. The data reported herein are from 134 adult burn patients without head injury or a history of thyroid disease and with serum TSH levels less than 20 μU/ml, from whom there were 656 samples taken without prior therapy with dopamine, corticosteroids, or other agents to support the cardiovascular system. Forty-five patients were nonsurvivors and died from 5–104 days after injury. Samples were also taken from 13 normal laboratory personnel.

The level of obtundation (LO) in the patients was determined at the time of sampling according to the system used by Rudman *et al.* (9) for patients with head trauma (Table 1). Serum T_4, T_3, T_3 charcoal uptake (T_3U), TSH (Diagnostic Products, Los Angeles, CA), and rT_3 (Serono, Milan, Italy) were determined in serum by RIA (radioassay for T_3U) with kits from the manufacturers. Indices of free T_4 and T_3 (FT_4I and FT_3I, respectively) were the product of the serum T_4 or T_3 level and T_3U divided by the T_3U value of the normal reference sample in the kit. T_3U was calculated as the tracer counts bound to the matrix divided by the total counts.

In the control and some of the burn samples, the dialyzable fractions of T_4 and T_3 after equilibrium at 37 C were determined at the Nichols Institute (San Juan Capistrano, CA). Free hormone concentrations (FT_4 and FT_3) were calculated as the product of the respective hormone concentration and the di-

Received September 29, 1984.
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TABLE 1. Determination of mental status

Criteria	Level of obtundation
Oriented to person and place, cooperative, not hallucinating (all true)	
no / yes	0
Conscious when undisturbed	
no / yes	1
Temporary arousal on minor disturbance	
no / yes	2
Semipurposeful movement on noxious stimuli	
no / yes	3
Deep tendon reflexes present	
no / yes	4
no	5

alyzable fraction. These samples were assessed with analysis of covariance to determine the correlations of FT_4I with FT_4 and FT_3I with FT_3 and assess any influence of burn injury on these relationships. The interrelationships among the measured variables within the larger group of burn patients (excluding data from nonburned subjects) were determined by stepwise multiple regression analysis (10). Survival was coded as 0, and death was coded as 1. In some cases, *t* tests were used to compare two independent means.

Results

Table 2 and Fig. 1 represent only the samples in which values for dialyzable fractions of T_4 and T_3 were available. Concentrations of T_4 and T_3 were depressed in burn patients, and the T_3U and dialyzable fractions were elevated. Nevertheless, the free indices (FT_4I and FT_3I) and free concentrations (FT_4 and FT_3) in the patients were also highly significantly depressed compared with normal values. Although in Table 2, the degree of depression of FT_4 appears almost equivalent to that of FT_4I, analysis of covariance indicates that in the patients, the FT_4I was relatively more depressed than was the FT_4 level (Fig. 1). The same relationships were evident between FT_3I and FT_3. Because it has been suggested that use of T_3U expressed as the matrix to serum ratio of tracer counts sometimes produces a better correlation between free indices and free concentrations than does

TABLE 2. Results in normal subjects and those burn patients in whom samples for equilibrium dialysis determinations were available

	Unburned normal (n = 13)	Burn survivors (n = 13)	Burn nonsurvivors (n = 3)
T_4 (μg/dl)	7.59 ± 0.35	3.52 ± 0.26[a]	1.84 ± 0.37
FT_4I	6.79 ± 0.25	3.56 ± 0.26[a]	1.90 ± 0.27
FT_4 (ng/dl)	2.14 ± 0.11	1.25 ± 0.08[a]	0.77 ± 0.13
T_3 (ng/dl)	141 ± 7.2	60 ± 7.2[a]	32 ± 9.0
FT_3I	126 ± 5.2	60 ± 7.4[a]	34 ± 8.6
FT_3 (pg/dl)	316 ± 12	200 ± 19[a]	146 ± 41
T_3U (%)	27.1 ± 0.7	30.7 ± 0.8[b]	33.1 ± 2.4
T_4DF (%)	0.0282 ± 0.0006	0.0361 ± 0.0007[a]	0.0440 ± 0.0021
T_3DF (%)	0.227 ± 0.008	0.347 ± 0.012[a]	0.471 ± 0.050
Age (yr)	34.1 ± 2.0	35.7 ± 5.3	66.3 ± 13.5
TBS (%)		34.4 ± 4.1	48.3 ± 9.2
PBD		13.5 ± 3.0	4.3 ± 2.0

Values are the mean ± SE. T_4DF, T_4 dialyzable fraction; T_3DF, T_3 dialyzable fraction. See text for definition of other variables. In five patients in whom two values for some variables were available, the mean of the two values was used.

[a] $P < 0.001$ *vs.* normal.

[b] $P < 0.01$ *vs.* normal.

T_3U expressed as the matrix to total ratio (4), the above results were reanalyzed employing T_3U expressed as the matrix to serum ratio. Since the results were the same, including the disproportionately greater depression of free indices relative to the free concentrations in burns, the free indices reported herein are based on the T_3U as the matrix to total ratio.

Figure 2 shows the hormone and LO values from the first 30 postburn days for patients in the full study group, arranged according to total burn size (TBS; as percentage of body surface area) and survival. The patterns for T_4 and T_3 depression in the burn patients were quite similar to those for FT_4I and FT_3I, respectively. Excepting values in the largest burn size group, mean T_4, T_3, FT_4I, and FT_3I (and LO in each group) were significantly different in nonsurvivors compared with values in survivors ($P < 0.01$). Figure 3 shows FT_4I and LO (restricted to patients with TBS of 30–60%) according to postburn day (PDB) in the first 3 weeks. Whereas FT_4I was lowest initially and rose in survivors during the first week, it remained low in nonsurvivors. LO worsened in nonsurvivors during the first week, and survivors had much less obtundation throughout. Both FT_4I and LO were altered in nonsurvivors for weeks before death and exhibited no additional deterioration in the weeks or days before death. Multiple regression analyses detected no relationship between days before death and FT_4I or LO. TSH values (mean ± SE; microunits per ml) were not significantly different between survivor (3.26 ± 0.12) and nonsurvivor (3.03 ± 0.30) samples (normal reference range, 0–10). All patients had TSH values less than 20, a practical limit below which TSH has been considered compatible with

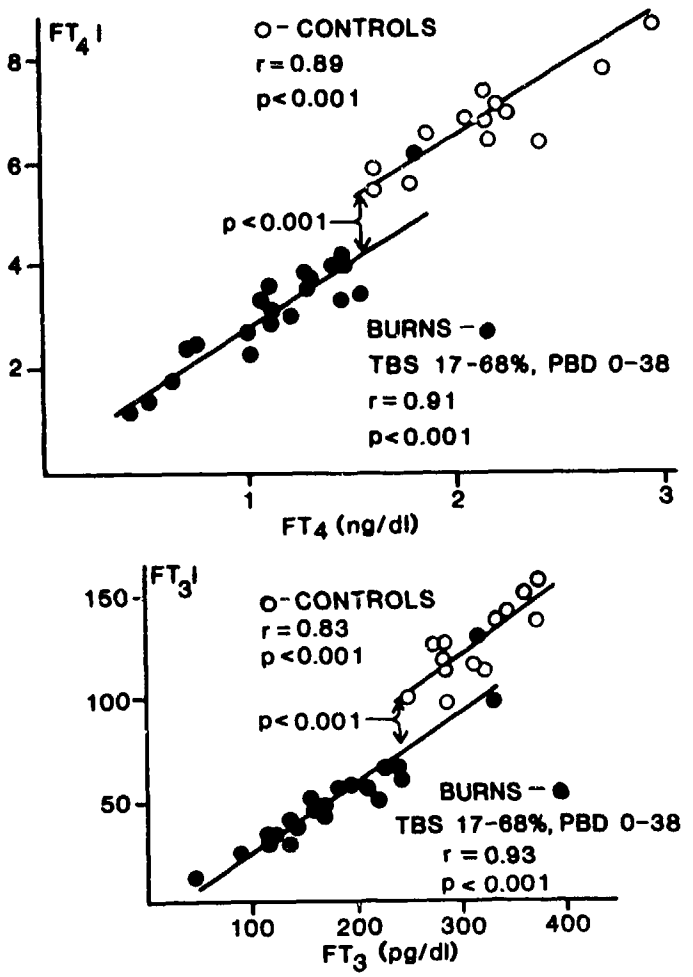

FIG. 1. Covariance analysis of free indices (FT_4I and FT_3I) and respective free concentrations (FT_4 and FT_3) of T_4 and T_3. Within each panel, the slopes did not differ between normal subjects and burn patients, so the lines have a common slope. The positional differences were significant, as indicated. Normal reference ranges: FT_4I, 5.5–14; FT_4, 1.32–3.8 ng/dl; FT_3I, 94–169; and FT_3, 230–660 pg/dl.

NTI (5).

Multiple regression analyses indicated that FT_4I was most strongly negatively (−) correlated with LO and that the residual variation in FT_4I was explained by further correlation with PBD (+), TBS (−), nonsurvival (−), and age (−) (all $P < 0.001$). LO correlated best with nonsurvival (+) and additionally with age (+), PBD (+), FT_4I (−), and FT_3I (−) (all $P < 0.001$). Nonsurvival was most strongly correlated with LO (+) and additionally with burn size (+) and FT_4I (−) (all $P < 0.001$). Other analyses were performed, excluding data collected within 24 h of administration of narcotics or tranquilizers, leaving 183 of the total 656 samples for analysis. FT_4I was lower with greater burn size, LO was higher in the nonsurvivors, and nonsurvival related separately to greater obtundation and lower FT_4I (all $P < 0.001$). Cimetidine was administered within 24 h before collection of 84 of the total 656 samples. After elimination of these 84 samples, multiple regression analyses of the remaining data still indicated correlation (all $P < 0.001$) of FT_4I with TBS and LO, of LO with survival, and of survival with LO and FT_4I.

Discussion

Depression of serum T_3 (1, 2, 3, 11) and T_4 (2, 3) and their free indices in burn patients has been reported previously. We confirm these findings, which are similar to those in other forms of NTI (4, 5). Further, we now report depression of mean serum FT_4 in burns, a finding similar to that reported in other forms of severe illness (12–14), though FT_4 may not always be depressed in NTI (4). Perhaps because of the possibility that circulating inhibitors of thyronine binding to circulating transport proteins in patients with NTI (15, 16) may inhibit binding to the matrix in the T_3U test (17), the FT_4I may exhibit a disproportionately greater reduction than that of the dialysis-based FT_4 concentration in these patients. Despite this discrepancy, patients with a wide variety of critical NTI and reduced serum T_4 concentrations reportedly had mean reductions not only of FT_4I but also of FT_4 (12–14). Thus, burn injury is similar to other severe NTI not only in causing reduction of mean total T_3 and T_4 concentrations, but also with respect to the presence of a defect in binding of thyronines in the circulation (elevated dialyzable fractions of T_4 and T_3), somewhat disproportionate lowering of free indices more than free concentrations, and a depressed mean FT_4 and FT_3. The previously reported absence of an increased concentration of TSH and its response to TRH or a frankly depressed TSH response to TRH in burn patients represents a further similarity with NTI (3). Burn injury may represent a good model of severe NTI.

Burn patients had depressed FT_4 and FT_3 levels and even more depressed FT_4I and FT_3I values as a group compared to values in normal subjects. However, there were proportional variations in FT_4I with FT_4 and in FT_3I with FT_3 in the burn patients tested and within a separate larger group of patients (3) not included in the present report. It is clear that among burn patients, those with lower FT_4I values also have lower FT_4 levels compared to FT_4 levels in those with higher FT_4I values, and the same applies to FT_3I and FT_3. Thus, variations in the free hormone indices within the overall group of burn patients in this study was considered to reflect variations in respective free concentrations. Among the hormones, nonsurvival correlated best with depression of FT_4I, suggesting lower FT_4 in nonsurviving compared to surviving burn patients. Among survivors of burns, lower T_4, FT_4I, T_3, and FT_3I were proportional to burn size, with values for nonsurvivors much lower at any given burn size below

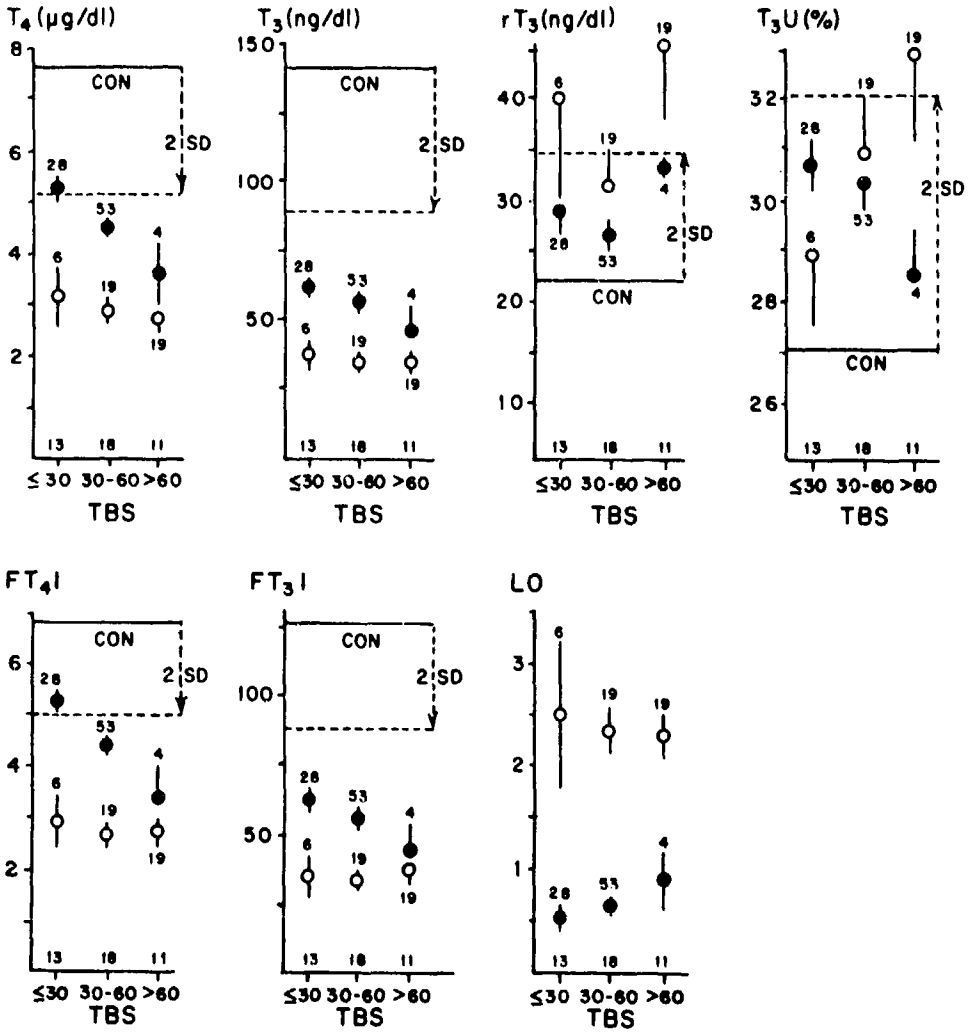

FIG. 2. Mean ± SE for measured variables during the first 30 PBDs in patients grouped according to burn size and outcome. In patients with more than 1 value for a variable, the mean value was used. The *numbers near the symbols* represent the number of patients. ●, Survivors; ○, nonsurvivors. The *values above the abscissa* are the mean number of days before death for sampling times in the nonsurvivors. The mean value for 13 normal subjects (CON) is shown (——), as is the extent of 2 SD from the normal mean (- - -).

60% or time after injury beyond the second day. Since all sampling was restricted to times when the patients were in the intensive care area, there was selection for patients who were more critically ill even among the survivors. This makes the FT_4I difference between nonsurvivors and survivors more noteworthy and probably explains the apparently blunted rise of FT_4I after the first week in the survivors.

In reports of other NTI (6, 18), low serum T_4 levels, sampled within 2 days of admission to intensive care units, occurred mainly in those patients who ultimately died. Kaptein *et al.* (7) found that in patients with various NTI admitted to intensive care units with low T_4 levels, T_4 returned toward normal in survivors, but not in nonsurvivors, and the patients' lowest T_4 value correlated negatively with mortality. Our finding of greater reduction of T_4 and FT_4I in nonsurviving burn patients than in survivors, manifested throughout their course, further indicates similarity between burn injury and other NTI. Calvano *et al.* (8) also found lower T_4 and FT_4I in nonsurviving than in surviving burn patients.

In patients with head trauma, serum T_4, FT_4, and T_3 were reduced in proportion to the degree of coma (9). It is interesting to note the reported difference in patients with coma due to head trauma exhibiting an elevated TSH response to TRH (9) compared to burn patients exhibiting a normal (or in nonsurvivors, a frankly blunted) TSH response (3). It is possible that in burns and other NTI, the metabolic milieu somehow suppresses the normal ability of thyrotrophs to recognize a deficiency of thyroid hormone and consequently augment their response to TRH. Perhaps this ability is not lost in patients whose pathological process may be a lesion restricted to the head and causing both coma and relative deficiency of endogenous hypothalamic TRH.

Reductions of mental status and of circulating T_4 can also be associated in the burn model of NTI. Greater reduction of FT_4I and mental status were both associated with mortality. Of course, one explanation of our results might be that these associations merely stem from otherwise unrelated parallel changes in FT_4I, LO, and mortality accompanying greater severity of injury. However,

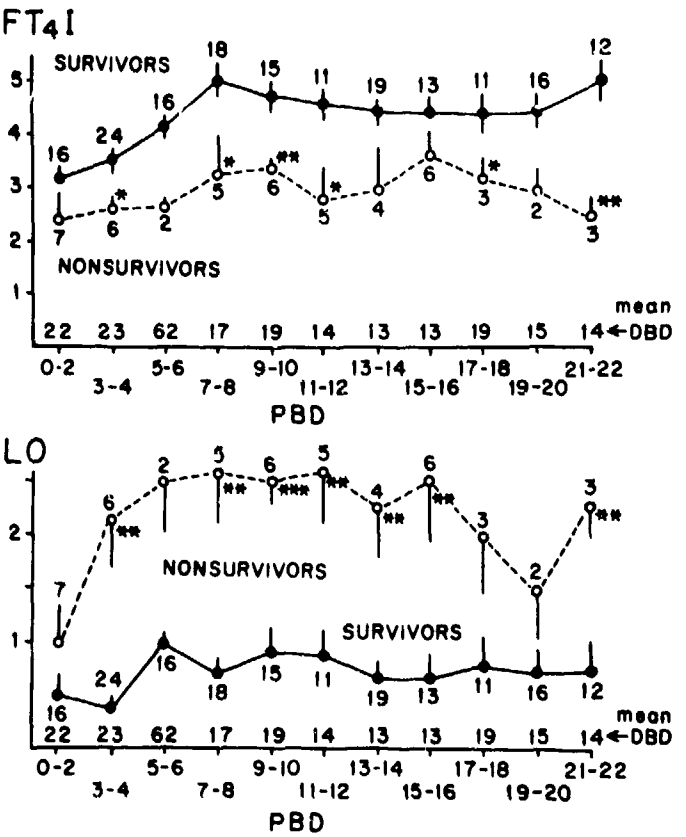

FIG. 3. Mean ± SE of FT_4I and LO for patients with TBS of 30–60% grouped by outcome and PBD during the first 3 weeks postinjury. The *numbers by the symbols* are the number of patients in each group. The *numbers above the abscissa* are the mean number of days before death (DBD) at which the samples were taken in nonsurvivors. *, $P < 0.05$; **, $P < 0.01$; ***, $P < 0.001$ (by t test; survivors *vs.* nonsurvivors).

regression analysis indicated variation in survival associated with variation in mental status and FT_4I after accounting for their common variation with burn size. Mean LO rose during the first week in nonsurvivors and remained elevated until death; their reduced FT_4I apparently preceded the reduction in mental status. The relationship of nonsurvival to FT_4I and LO did not depend upon administration of iodine, dopamine, corticosteroids, narcotic analgesics, or tranquilizers. Thus, we think it is reasonable at least to consider an alternate hypothesis for our results, in which persistently reduced circulating T_4 might have contributed to defective central nervous function and, possibly, to mortality. The measurement of obtundation is nonspecific, and further studies are necessary to test directly whether a deficiency of T_4 available to the brain in fatal NTI can contribute to either a pathophysiologically significant local deficit of hormone in that tissue or death.

Acknowledgments

We wish to thank James Bullard, Len Seraile, and Sandy H. Coggins for technical and editorial assistance.

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